REMARKS

Claims 1, 4-6, 11-23, 25-33 and 37-52 are pending in the present application. Claims 43-52 have been withdrawn from examination as being drawn to nonelected subject matter. Claims 1, 4-6, 11-23, 25-33 and 37-42 were variously rejected under 35 U.S.C. § 103.

By this amendment, claim 12 has been canceled, claims 1, 11, 37 and 40 have been amended and claim 53 has been added, without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification as described below. Support for new claim 53 is found, *inter alia*, in original claim 12 and at page 15, lines 19-27.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Attached hereto is a marked-up version of the changes made to claims by the current amendment. The attached page is entitled "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Applicants thank Examiners Foley and Housel for the helpful discussion and claim language suggestion during a telephonic interview with Applicants' representative on January 17, 2003.

Applicants have carefully considered the points raised in the Advisory Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Claim amendments

The claims have herein been amended to explicitly recite that the second antigen is not proximately associated with the complex comprising the polynucleotide and the first antigen. Implicit support for this amendment is found throughout the specification. For example, nowhere in the specification is the second antigen described as being administered in proximate association with the polynucleotide-first antigen complex, although administration of an ISS-containing polynucleotide proximately associated with the first antigen is described throughout the specification. In addition, the second antigen is not proximately associated with the polynucleotide-first antigen complex in the any of the experimental examples in the specification.

The specification also describes methods of the invention in which administration of the substances is such that the second antigen cannot be administered in proximate association with the polynucleotide-first antigen complex. For example, at page 15, lines 19-27 and page 55, Table 6, the specification describes the administration of the immunomodulatory polynucleotide and first antigen to a site which is different from the site of administration of the second antigen. Accordingly, the second antigen is not in proximate association with the polynucleotide or with the first antigen in this administration protocol. The specification also describes methods of modulating an immune response to a second antigen in which the second antigen is encountered by an environmental exposure. In such a method, the second antigen would not be proximately associated with the polynucleotide-first antigen complex.

Accordingly, Applicants submit that the amendments are supported by the specification as filed.

Rejections 35 U.S.C. §103

Claims 1, 4-6, 11-23, 25-33 and 37-42 were variously rejected under 35 U.S.C. § 103 as follows. Claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33 and 40-42 were rejected under 35 U.S.C.

103(a) as allegedly being unpatentable over Schwartz et al. (WO 98/55495, "Schwartz"). Claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33 and 40-42 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Carson et al. (WO 98/16247, "Carson"). Claim 5 was rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson further in view of Rose (*J. Ther. Biol.* 195:111-128 (1998)). Claims 15 and 38 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson and Rose further in view of Lee et al. (*Ann. Med.* 30:460-468 (1998), "Lee"). Claims 16 and 39 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson and Rose further in view of Durali et al. (*J. of Virol.* 72(5):3547-3553 (1998), "Durali"). Claims 18 and 19 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson, Rose, Lee, and Durali further in view of Anderson (US Patent No. 4,673,574). Claim 37 was rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson, Rose, Lee, Durali, and Anderson.

Applicants respectfully traverse these rejections.

The amended claims are directed to a method of modulating an immune response to a second antigen through co-administration of (i) a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen and (ii) a second antigen, where the amount of the polynucleotide-first antigen complex administered is sufficient to modulate an immune response to the second antigen. In the claimed method, the second antigen is not proximately associated with the polynucleotide-first antigen complex. The claimed invention is also directed to a composition comprising (i) a complex comprising an immunomodulatory polynucleotide proximately associated with a viral conserved polypeptide (first antigen) and (ii) a viral variable polypeptide (second antigen) and to a composition comprising (i) a complex comprising an immunomodulatory polynucleotide proximately associated with an allergen (first antigen) and (ii) a second antigen. In the claimed compositions, the second antigen is not proximately associated with the polynucleotide - first antigen complex.

Claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33 and 40-42 over Schwartz.

Schwartz describes the use of compositions in which an immunostimulating oligonucleotide and an antigen are in proximate association to modulate or enhance an immune response to the antigen. Schwartz teaches that for an enhanced immune response to an antigen, including a Th1 response, an ISS-containing oligonucleotide and the antigen should be in proximate association with each other as opposed to being freely soluble in solution with each other.

Accordingly, Schwartz does not teach the claimed invention. Schwartz does not teach or suggest co-administration of (i) a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen with (ii) a second antigen, where the second antigen is not proximately associated with the complex and where the amount of the complex administered is sufficient to modulate an immune response to the second antigen.

The Examiner states that "[i]t appears from the arguments presented that applicant intends for the claims to specify that the second antigen is in a mixture and is not proximately associated with the ISS-first antigen conjugate. This limitation is not clearly recited in the claims, if this is what applicant intends." Advisory Action, paragraph bridging pages 2 and 3.

Applicants respectfully note that the amended claims explicitly recite that the second antigen is not proximately associated with the complex comprising the polynucleotide and the first antigen.

Applicants also respectfully point out that, contrary to the Examiner's statement, the claimed methods are not limited to administration of a "mixture" containing the second antigen along with the polynucleotide-first antigen complex. As described in the specification, for example, at page 13, lines 12-15, "co-administration" in the claimed method refers to the timing of administration of the complex and the second antigen. Thus, the claimed method includes co-administration of the complex and the second antigen as separate solutions or compositions. The claimed invention also provides for administration of the polynucleotide-first antigen complex to

a site which is different from the site of administration of the second antigen. See, for example, claim 12, herein canceled and re-presented as new claim 53.

The Examiner also states that Schwartz "teaches multiple ISS-antigen conjugated molecules that comprise different antigens and also administration of an antigen mixture" and in support, points to Example 3 of Schwartz as being "drawn to co-administration of an antigen-ISS conjugate and freely associated adjuvant MF59." Advisory Action, page 3.

Applicants respectfully disagree with the interpretation the adjuvant MF59 as an antigen in Schwartz.

Schwartz refers to MF59 as an adjuvant (Example 3) and defines adjuvant as "a substance which, when added to an immunogenic agent, nonspecifically enhances or potentiates an immune response to the agent in the recipient host upon exposure to the mixture." Schwartz, page 13, lines 6-8, emphasis added. Schwartz defines "antigen" as "a substance that is recognized and bound specifically by an antibody or by a T cell antigen receptor." Schwartz, page 12, lines 39-40, emphasis added.

Thus, Schwartz clearly distinguishes an antigen from an adjuvant by the different type of immune responses each stimulate.

Applicants respectfully submit that Schwartz by indicating that MF59 is an adjuvant does not convey to the skilled artisan that MF59 is an antigen. Accordingly, Example 3 of Schwartz does not teach or suggest the administration of a second antigen with a complex comprising an immunomodulatory polynucleotide and first antigen as claimed.

Applicants further submit that nothing in Schwartz teaches or suggests the claimed invention. As outlined in the response to the final Office Action filed October 23, 2002, Applicants respectfully submit that there is no suggestion or motivation in the reference, or in the art, to modify Schwartz to arrive at the claimed invention. Applicants further submit that Schwartz provides no reasonable expectation of success of the claimed invention.

Thus, Schwartz does not support *prima facie* obviousness with regard to the claimed invention.

Claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33 and 40-42 over Carson.

Carson describes immunomodulatory compositions in which an ISS-containing polynucleotide is linked to an antigen. Upon administration of the compositions, a Th1 immune response specific to the antigen linked to the ISS-containing polynucleotide is stimulated.

Carson does not teach or suggest co-administration of (i) a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen and (ii) a second antigen, where the second antigen is not proximately associated with the complex and where the amount of the complex administered is sufficient to modulate an immune response to the second antigen.

The Examiner acknowledges that in Carson "it is evident that an immuno-potentiation of an antigen occurs when it is conjugated with an ISS molecule" and that Carson "teaches that when unconjugated ISS and a freely associated antigen are coadministered, a potentiation of an immune response is not observed." Advisory Action, page 4. The Examiner then states that "the claims are not limited to un-conjugated second antigen."

Applicants respectfully note that the amended claims explicitly recite that the second antigen is not proximately associated with the complex comprising the polynucleotide and the first antigen.

As outlined in the response to the final Office Action filed October 23, 2002, Applicants respectfully submit that Carson does not teach or suggest the claimed invention. Nor is there any suggestion or motivation in Carson, or in the art, to modify the teachings of Carson to arrive at the claimed invention. Finally, Carson provides no reasonable expectation of success of the claimed invention.

Accordingly, Carson does not support *prima facie* obviousness with regard to the claimed invention.

Claim 5 over Schwartz or Carson further in view of Rose.

As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention. Neither Schwartz or Carson describe co-administration of (i) a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen with (ii) a second antigen, where the second antigen is not proximately associated with the complex and where the amount of the complex administered is sufficient to modulate an immune response to the second antigen.

The secondary reference Rose describes platform molecules and the use of platform molecules to link various agents in the treatment of cancer. Rose does not supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary reference do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Claim 15 and 38 over Schwartz or Carson and Rose further in view of Lee.

Claims 15 and 38 are directed to a method and a composition of the invention in which the first antigen is influenza nucleocapsid protein. As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention and the claimed invention is not obvious over

Schwartz or Carson. Also, as discussed above, the claimed invention is not obvious over Schwartz or Carson further in view of Rose. Lee describes that ISS within DNA vaccines result in a Th1 immune response to the encoded antigen and describes the use of DNA vaccines encoding influenza proteins in tests for infection protection.

Neither Rose or Lee, alone or in combination, supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen, where the second antigen is not proximately associated with the complex. Also, none of the references, either alone or in combination, describes or suggests the composition as claimed.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Claims 16 and 39 over Schwartz or Carson and Rose further in view of Durali.

Claims 16 and 39 are directed to a method and a composition of the invention in which the first antigen is HIV gag protein. As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention and the claimed invention is not obvious over Schwartz or Carson. Also, as discussed above, the claimed invention is not obvious over Schwartz or Carson further in view of Rose. Durali describes production of cytotoxic T lymphocytes against HIV antigens from various HIV clades.

Neither Rose or Durali, alone or in combination, supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary

references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen, where the second antigen is not proximately associated with the complex. Also, none of the references, either alone or in combination, describes or suggests the composition as claimed.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Claims 18 and 19 over Schwartz or Carson, Rose, Lee and Durali further in view of Anderson.

Claim 18 is directed to a method of the invention in which the first antigen is diphtheria toxin mutant (CRM197). Claim 19 is directed to a method of the invention in which the first antigen is diphtheria toxoid. As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention and the claimed invention is not obvious over Schwartz or Carson. Also, as discussed above, the claimed invention is not obvious over Schwartz or Carson further in view of Rose, Lee and Durali. Anderson describes diphtheria toxoid and diphtheria CRM 197 as carriers in vaccine preparations.

Rose, Lee, Durali and/or Anderson, alone or in combination, do not supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a

complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen, where the second antigen is not proximately associated with the complex.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Claim 37 over Schwartz or Carson, Rose, Lee, Durali and Anderson.

Claim 37 is directed to a composition of the invention comprising (i) an ISS-containing immunomodulatory polynucleotide proximately associated with a viral conserved polypeptide and (ii) a viral variable polypeptide. As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention and the claimed invention is not obvious over Schwartz or Carson. Also, as discussed above, the claimed invention is not obvious over Schwartz or Carson further in view of Rose, Lee and Durali. Anderson describes diphtheria toxoid and diphtheria CRM 197 as carriers in vaccine preparations.

Rose, Lee, Durali and/or Anderson, alone or in combination, do not supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen, where the second antigen is not proximately associated with the complex.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

CONCLUSION

Applicants believe that all issues raised in the Advisory Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882000800. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: January 23, 2003 By: Karen R Zachow

Karen R. Zachow
Registration No. 46,332

Morrison & Foerster LLP
3811 Valley Centre Drive - Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5191
Facsimile: (858) 720-5125

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the following amendments without prejudice or disclaimer.

In the Claims:

Please amend claims 1, 11, 37 and 40 as follows.

1. (Twice Amended) A method of modulating an immune response to a second antigen in an individual, comprising [administering] co-administering to the individual

(i) a complex comprising an immunomodulatory polynucleotide [comprising an immunostimulatory sequence (ISS) and] proximately associated with a first antigen [with] and

(ii) a second antigen,

wherein the polynucleotide comprises an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5'-cytosine, guanine-3', wherein the [polynucleotide and first antigen are] second antigen is not proximately associated with the complex, and wherein the [polynucleotide and first antigen] complex is [are] administered in an amount sufficient to modulate an immune response in the individual to the second antigen.

11. (Twice Amended) The method of claim 1, wherein the complex [immunomodulatory polynucleotide and first antigen] and the second antigen are administered at the same site in the individual.

37. (Twice Amended) A composition comprising

(i) a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen and

(ii) a second antigen,

wherein the polynucleotide comprises an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5'-cytosine, guanine-3', wherein the second antigen is not

proximately associated with the complex, and wherein the first antigen is a viral conserved polypeptide and the second antigen is a viral variable polypeptide.

40. (Amended) A composition comprising

(i) a complex comprising an immunomodulatory polynucleotide proximately associated with a first antigen and

(ii) a second antigen, wherein the polynucleotide comprises an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5'-cytosine, guanine-3', wherein the second antigen is not proximately associated with the complex, and wherein the first antigen is an allergen.